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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/999,690	09/08/97	GUNZBURG W	GSF97-03A

HM22/0814
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EXAMINER	
LI,Q	
ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	08/999,690	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The request for reconsideration filed on July 21, 2001 has been entered and assigned as Paper #19. No claim is amended. Claims 1-52 are pending and under current examination.

The Remarks in response to Office action (paper #17) has been carefully considered a complete response to the Remark follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

The prior rejection to claims 1-52 stands for the reasons advanced on pages 2-5 of the prior Office action (paper No. 17).

The claims recite "*therapeutic antimicrobial peptide or a biologically active derivative which is a part, analogue or homologue of the antimicrobial peptide*" The claims as written encompass a large number of known or unknown antimicrobial peptides having antimicrobial property.

Applicants argue that the court has clearly stated that a specification need not describe what is well-known in the art, and it has provided adequate written description of characteristic features and structural changes that influence the biological activity of

AMP derivatives, citing the description to melittin, and cecropin analogues in page 4, lines 7-14, and page 9, lines 24 to 30 of the instant specification. Furthermore, applicants argue that at the time of the invention, methods of obtaining a biologically active derivative is known to those of skill in the art, and a substantial amount of information in this field of art is readily available for making and assessing analogues or homologues of an antimicrobial peptide.

The argument has been carefully considered, but found not persuasive.

First, the Revised Interim Guidelines for "Written Description" requirement states: "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

Secondly, as Paper #17 indicated, melittin is only one species of the antimicrobial peptide family, which encompass a wide range of endogenously secreted peptides including lytic peptides and conventional antibiotics. (page 3, 2nd paragraph). *Boman* (see citation in papers #9, #17) teaches antimicrobial peptides embrace all animal peptide antibiotics, made by any animal including human. Milittin is a basic polypeptide from the venom of the honey bee, its structure and function is relatively well-studied, even such, there is still quite significant variations as evidence by *Perez-Paya's* teaching as cited in Paper #17, and the experimental data in the instant

specification. In analyzing whether the written description requirement is met for the claimed subject matter as a genus of antimicrobial peptides, a representative number of species has to be disclosed by their complete sequences, structure, and other relevant identifying characteristics. The genus encompasses any peptide which inhibits the growth of a microorganism secreted by any animal, thus encompassing an uncountable number of possible peptides and derivatives. Considering the potential peptides that would be encompassed by the claims, the exemplary embodiments are not the representative species of the genus.

Thirdly, even within the species of melittin, significant variations concerning the structure-functional relationship have been observed both in the teachings of those skilled in the art and the exemplary embodiment of the instant specification. The details are set forth advanced in Paper #17, pages 3-5.

Applicant is referred to the Revised Interim Guidelines for "Written Description" requirement published December 21, 1999 in the Federal Register, Volume 64, Number 244, pages 71427-71440. "Possession may be shown in any number of ways. Possession may be shown by actual reduction to practice, by a clear depiction of the invention in detailed drawings...or by a written description of the invention describing sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention." (page 71435, middle column, first paragraph of "a") The skilled artisan cannot envision the detailed chemical structure of the genus of the encompassed molecules that inhibits a microorganism, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere

statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the limited disclosure in the specification to melittin and its analog could not be extend to derivatives of *any* and *all* types of antimicrobial peptides, secreted by *any* and *all* animals which are less studied, relatively unknown, or waiting to be discovered. In summary, the specification has not set forth in terms of structural or distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed genus of the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession

of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of derivatives of *all* peptides that inhibit a microorganism.

For the reasons of record and those set forth above, only the described SB-37, Shiva-1, and the described melittin analog meet the written description provision of 35 U.S.C. §112, first paragraph.

With respect to the new matter rejection advanced on page 6, 2nd and 3rd paragraph of Paper #17, applicants argue that there is no requirement that Applicants provide a reason for the amendment, and citing case law to support the argument, this is non-responsive.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY **NOT PRESENT IN THE APPLICATION AS FILED**, INVOLVING A DEPARTURE FROM, ADDITION TO, OR **DELETION** FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED.

APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE" (emphasis added). However, applicants have not done so to specifically point out the support for the amendment in the specification, therefore, the new matter is introduced. Applicant is required to cancel the new matter in response to this Office action.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

With respect to the new matter rejection advanced on page 6, 2nd and 3rd paragraph of Paper #17, applicants argue that there is no requirement that Applicants provide a reason for the amendment, and citing case law to support the argument, this is non-responsive.

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ENABLEMENT REQUIREMENT

The prior rejection to claims 1-52 stands for the reasons advanced on pages 3-6, Paper #9; and pages #5-8, Paper #17 of the prior Office action.

Particularly, the specification, while being enabling for making an analog or homologue of melittin and ceropins having anti-microbial and anti-tumor activities *in vitro* and *in vivo* in an animal model, does not reasonably provide enablement for making and using analogs or homologues of *the genus of* antimicrobial peptides, treating any and all diseases selected from the group consisting of : a genetic defect, cancer and viral infections. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argue that the specification provides guidance for making analog and homologue of an antimicrobial peptide, thus, the claims are enabled. However, the claims read on a genus of antimicrobial peptides including parts, analogue or homologue and combinations thereof, the specification fails to provide sufficient

guidance regarding how to make a partial or combination, an analogue or homologue for any and all AMPs, whether the specific embodiment of the invention would apply to any and all antimicrobial peptides, what are the structures of these peptides and what structural change it would tolerate so that the derivatives will still be capable of killing microorganisms.

The claimed invention additionally reads on therapeutic methods treating disease in humans and animals. Applicants explained the reasons of variations in their experimental data, and argued that the construct was successfully delivered, the AMP was expressed in vitro and in vivo in an acceptable animal model and produced antitumor and antiretroviral effects with a degree of safety, therefore met their burden under 35 U.S.C. 112, first paragraph.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

With respect to the claim breadth, the standard under 35 U.S.C. §112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. The specification teaches to use the vehicle construct for gene therapy, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses gene therapy for disease

treatment including prevention, alleviating and curing a disease associated with a genetic defect, cancer, and viral infection.

In view of the state of the art, the gene therapy for cancer, viral and hereditary diseases are still under development, and highly unpredictable as taught by numerous teachings cited in Papers #9 and #17. The animal model may be acceptable for experimental test, but not well correlated with human diseases for reasons explained in Paper #17. Furthermore, it takes more than the expression of a potentially therapeutic gene to achieve the goal of gene therapy, it requires long term stable expression of the transgene in a significant population of appropriate cells and the appropriate response of the target cells to the transgene. These are some of the reasons why the promising potential of gene therapy has not met with the expectations in reality. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed vector and experimental studies, it is not enabled for its full scope because the specification does not disclose which genetic defective disease the method could be used to treat, any therapeutic effect in an established tumor, any therapeutic effect in an established *in vivo* infection, the lasting effects, the treatment regimen, etc. the cytotoxic effect is only one aspect that one would encounter to practice the claimed invention and would look for guidance in the specification. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for executing gene therapy for cancer and viral

infection, which awaits further development to the practical level. Based upon the limited disclosure, the unpredictability of the art, the level of the skill, and the breadth of the claims, one skill in the art would have been required to perform undue experimentation to practice the invention.

Applicants further cite *Marzocchi* to argue that "it is incumbent upon the Patent Office wherever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertion of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. It is noted that *Marzocchi* also teaches "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC". When instant claims read on a method for the treatment of any disease associated with a genetic defect, cancer, and viral infections, a doubt is reasonable since there is no universal cure for these diseases as of today. Furthermore, the Office has provided numerous teachings such as *Verma, Orkin, Bowman,* and *Perez-Paya et al* to illustrate the state of the art and the levels of those skilled artisans to indicate the doubt is reasonable. Thus, it is applicants' duty to provide sufficient teaching to enable the claimed invention.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

Conclusion

No claim is allowed. Claims 1-52 are free of the cited prior art of record, however, they are subject to other rejections.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 410-308-7942. The examiner can normally be reached on 8:30 am - 5 pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are 410-308-4242 for regular communications and 410-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

QJL
August 13, 2001

Karen M. Hauda

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